Aldosterone in Diabetic Kidney Disease

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Agenda

- Overview on diabetic nephropathy.
- Role of aldosterone in pathogenesis of diabetic nephropathy.
- Aldosterone antagonism.
- Aldosterone and renal tubular acidosis.

Definition of Diabetic Nephropathy

Diabetic nephropathy is a clinical syndrome characterized by the following:

- Persistent albuminuria (>30 mg/d or >20 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate.
- Elevated arterial blood pressure.

- Longstanding History of diabetes ± retinopathy.
- Renal Biopsy confirmation is rare

Interpretation of albuminuria results

DKD is often present if:

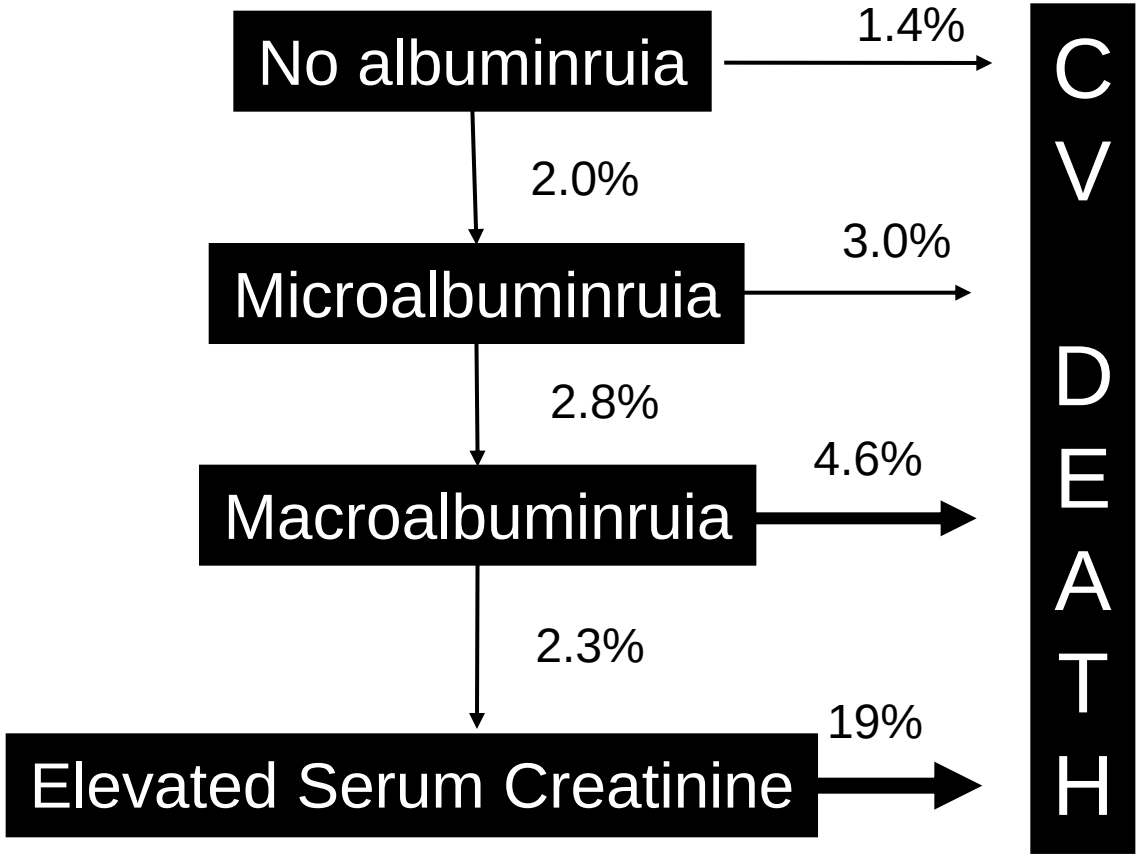
- A3: more than 300
- A2: 30 - 300
  - Presence of retinopathy
  - in type 1 diabetes, duration at least 5 -10years

Interpretation of albuminuria results

DKD may not be present if:

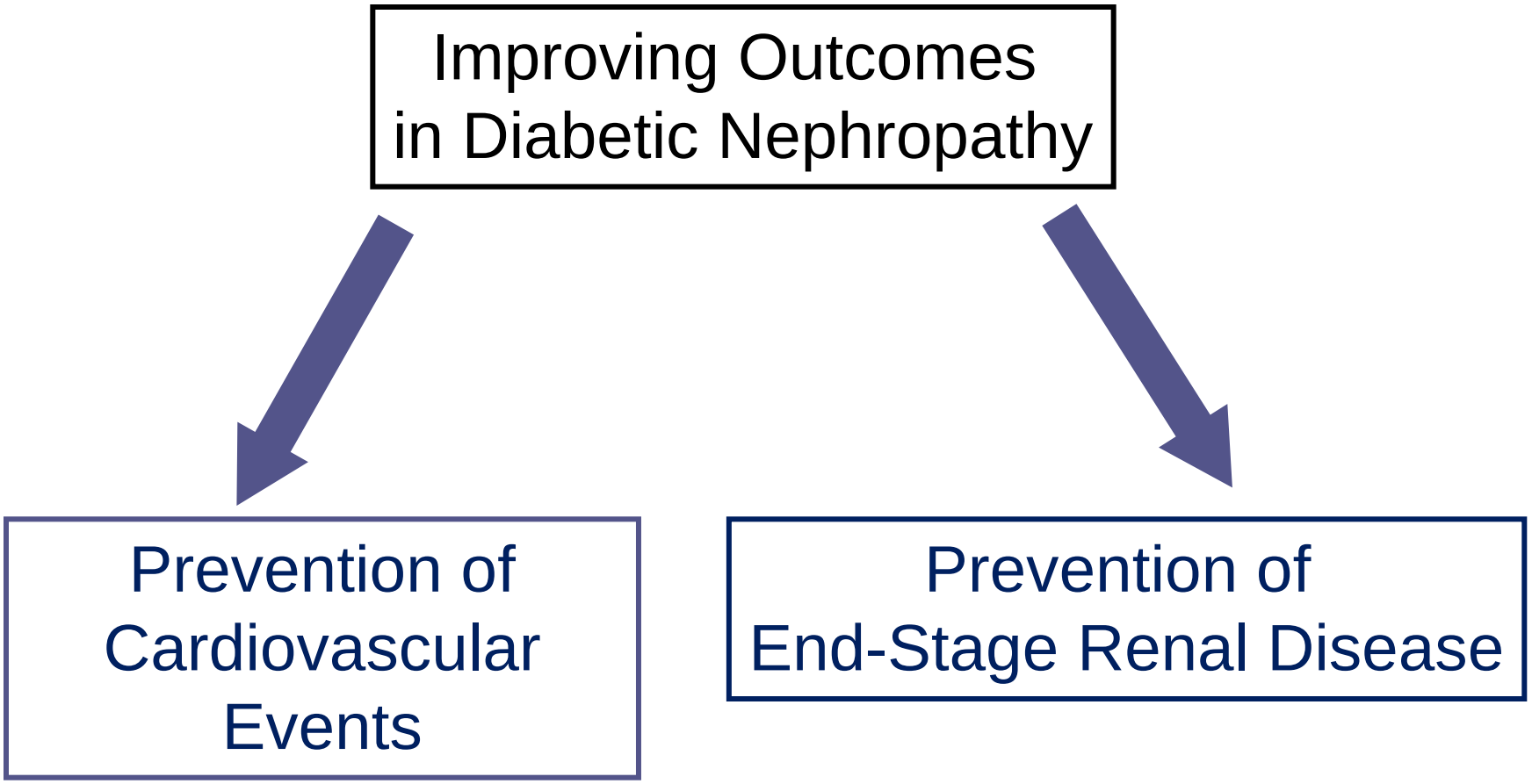
- Absence of diabetic retinopathy.
- Rapid decline in GFR (1>ml/min per month).
- Sudden onset of nephrotic syndrome.
- Refractory hypertension.
- Active urinary sediment (hematuria).
- Signs or symptoms of systemic disease.
- >30% reduction in GFR after starting RAS blockade.

The United Kingdom Prospective Diabetes Study (approx. 5000 Type 2 Diabetics)
Newly diagnosed, predominantly white, medically treated

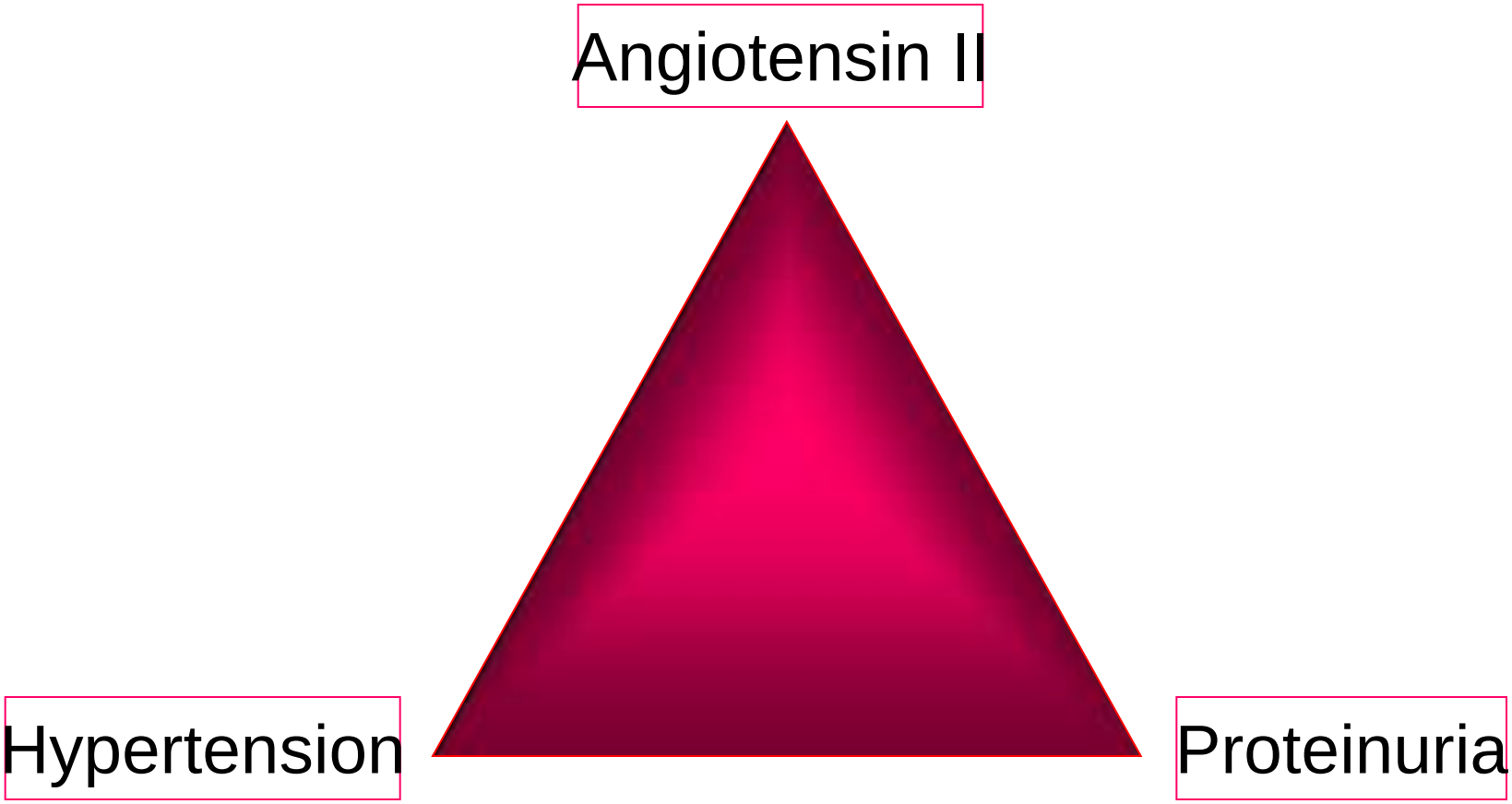


Adler et al. *Kid Int, 2003*

Diabetic Nephropathy



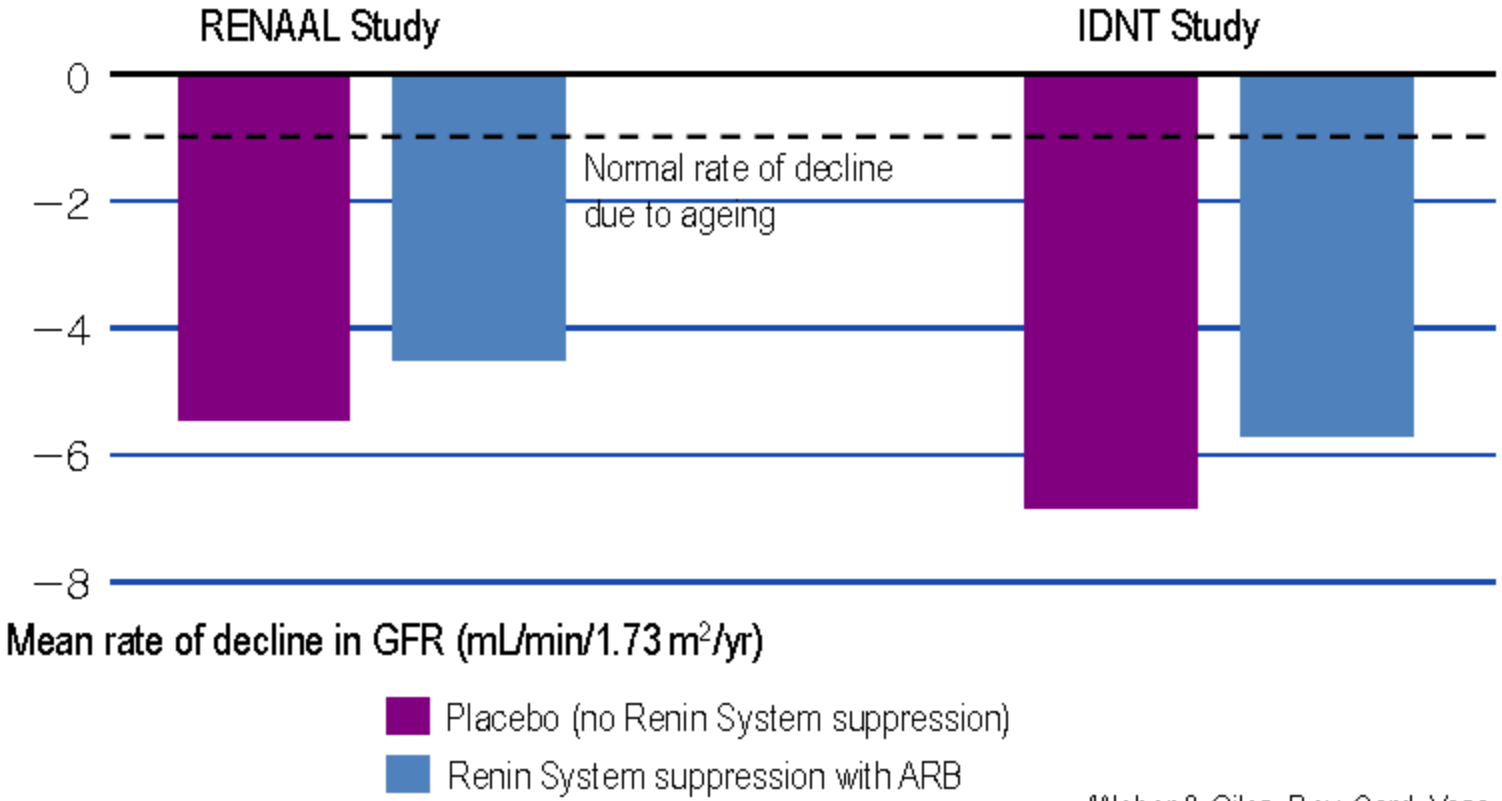
The Renal Injury Triad



Diabetic Nephropathy: **Management:**

- Lower blood pressure.
- Reducing Proteinuria
- Inhibition of Renin-Angiotensin System
- Multiple risk factor intervention
  - Glycemia
  - Dyslipidemia
  - Physical activity
  - Aspirin
  - Smoking cessation

Existing antihypertensives have limitations: Despite treatment with ARBs, the rate of decline in renal function is still higher than expected due to ageing

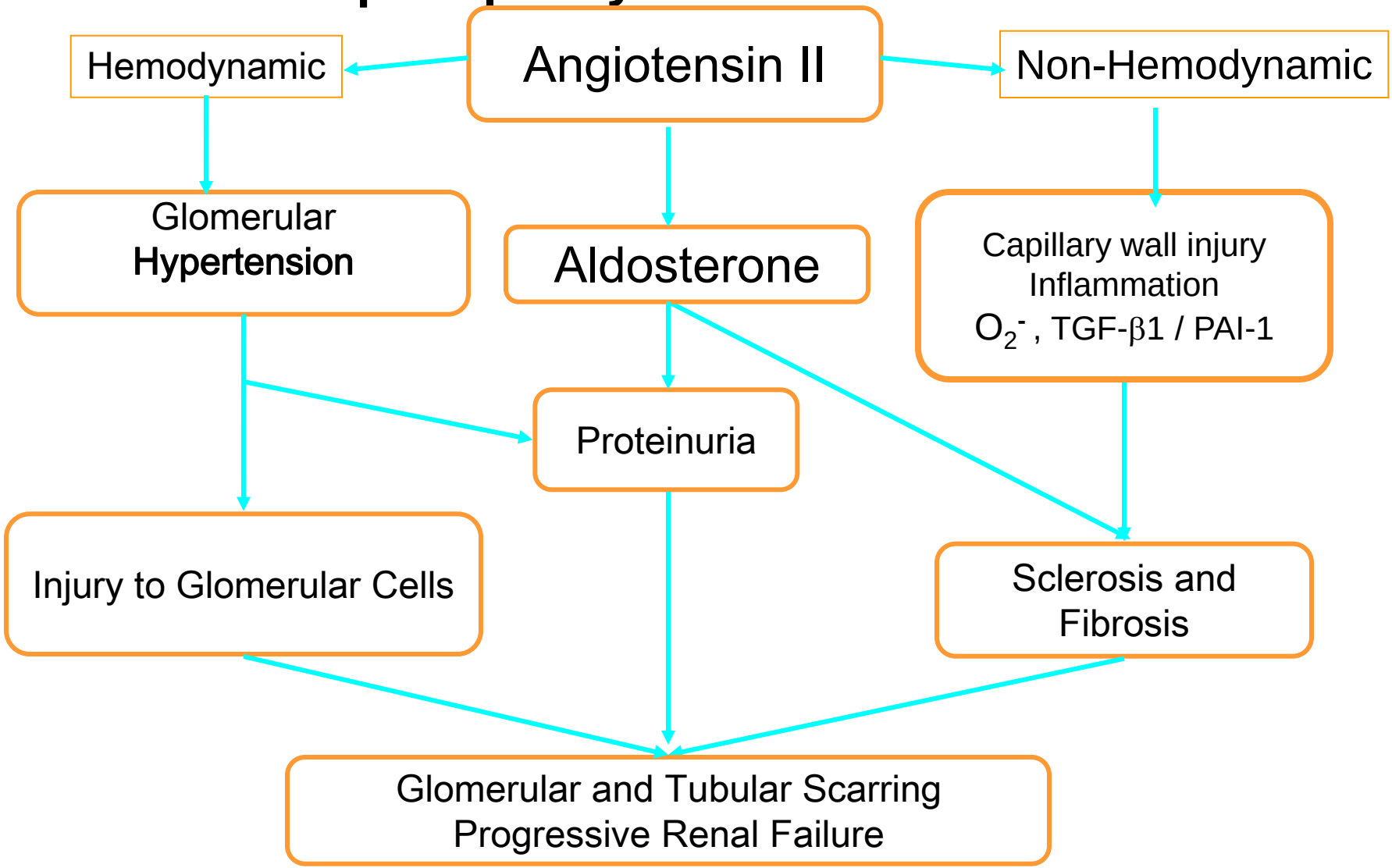


(Weber & Giles, Rev. Card. Vasc. Med. 2006)

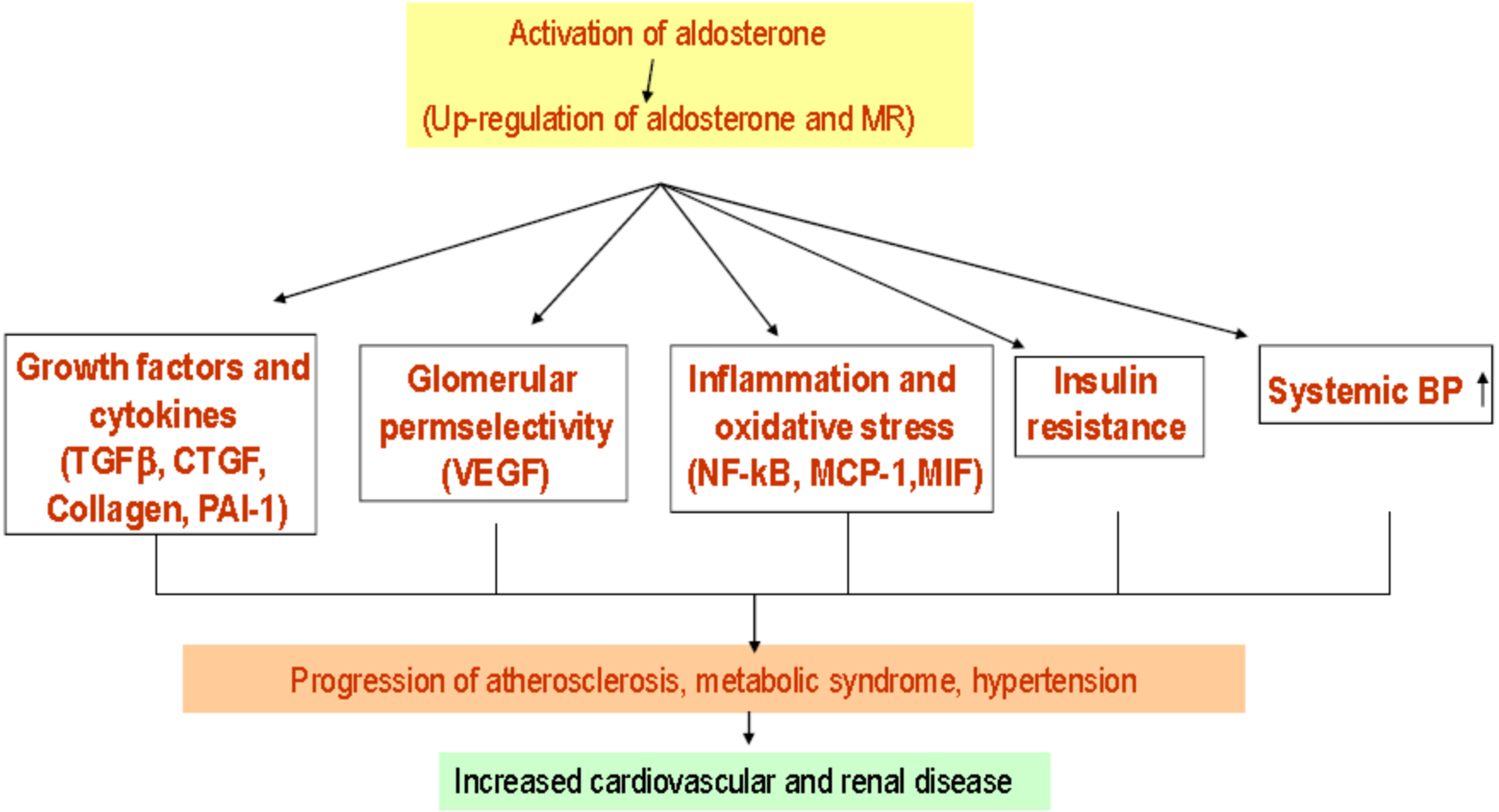
Role of aldosterone and its inhibition in the progression of diabetic nephropathy


Aldosterone
an old friend and new comer

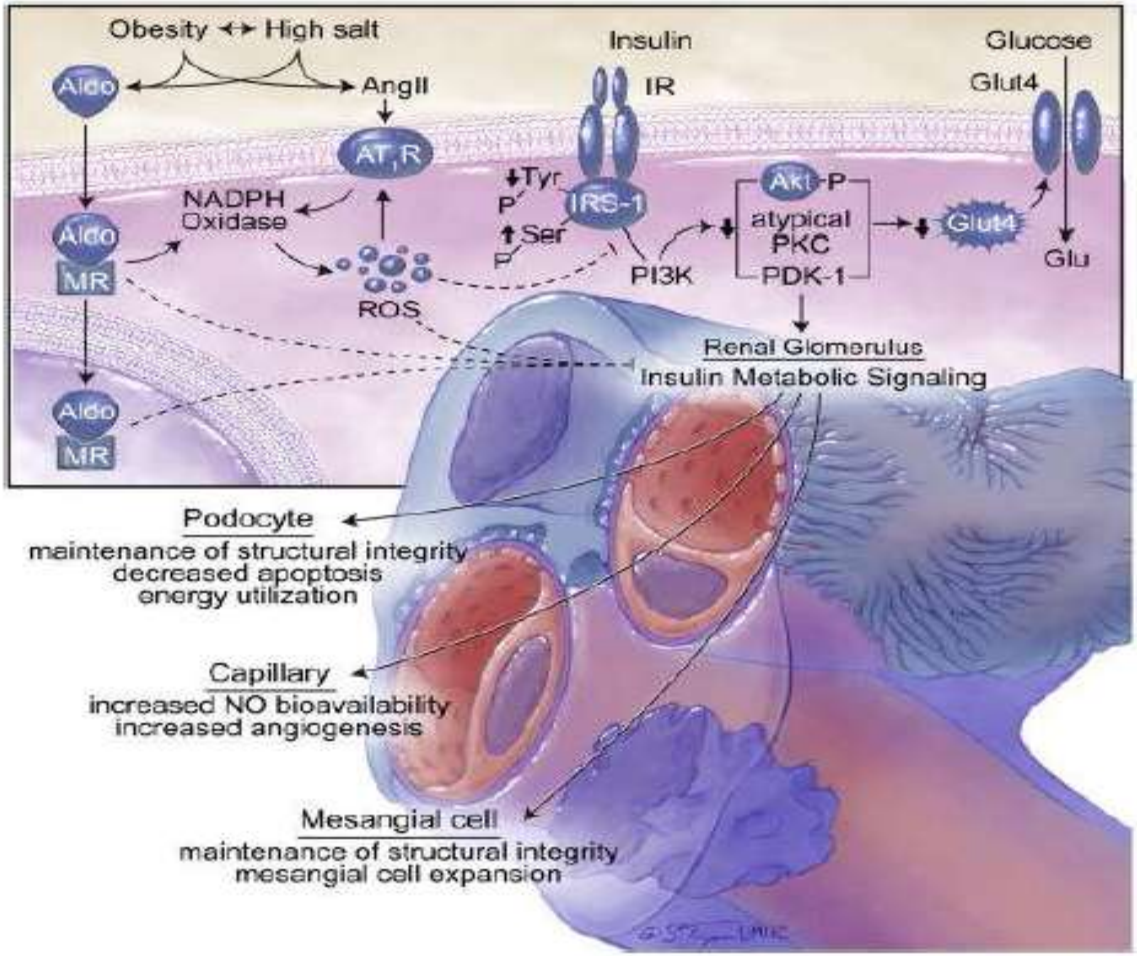
Role of Aldosterone in the Pathogenesis of Diabetic Nephropathy



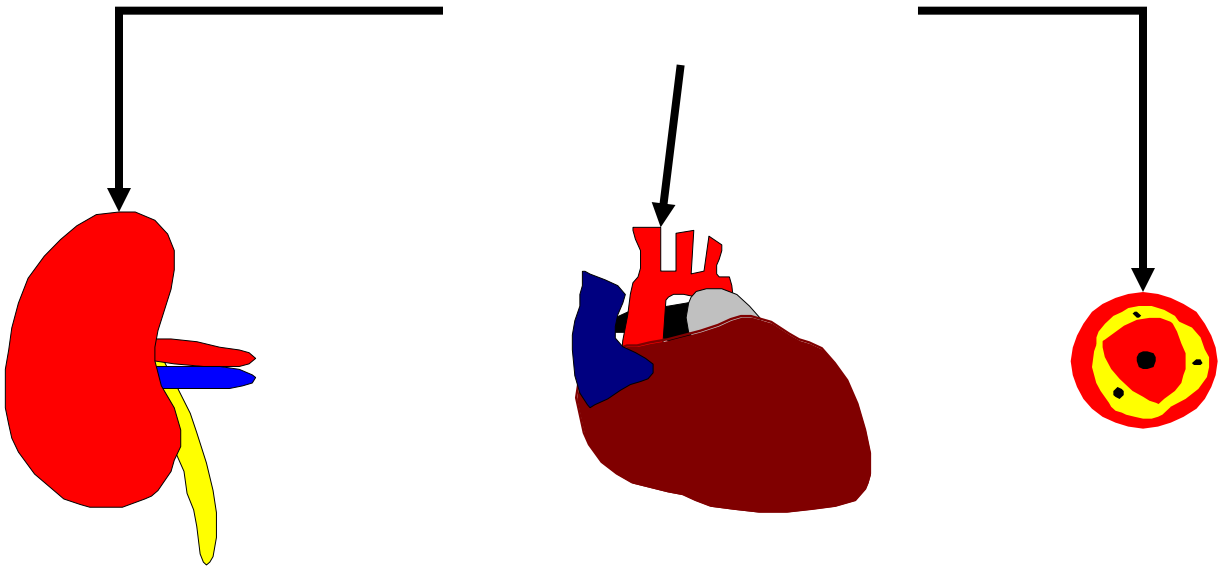
New aspect of aldosterone in diabetic nephropathy



Aldosterone (Aldo) and Angiotensin II (Ang II) actions on Glomerular Insulin Metabolic Signaling



Adverse Renal and Cardiovascular Effects of Aldosterone



Glomerulosclerosis
Interstitial Fibrosis
Proteinuria
Renal Failure

Ventricular Hypertrophy
Cardiac Fibrosis
Contractile Dysfunction
Heart Failure

Endothelial dysfunction
Inflammation
Oxidative Stress

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Role of Aldosterone in Renal Vascular Injury in Stroke-Prone Hypertensive Rats

Ricardo Rocha, Praveen N. Chander, Andrea Zuckerman and Charles T. Stier, Jr.

Hypertension. 1999;33:232-237
doi: 10.1161/01.HYP.33.1.232
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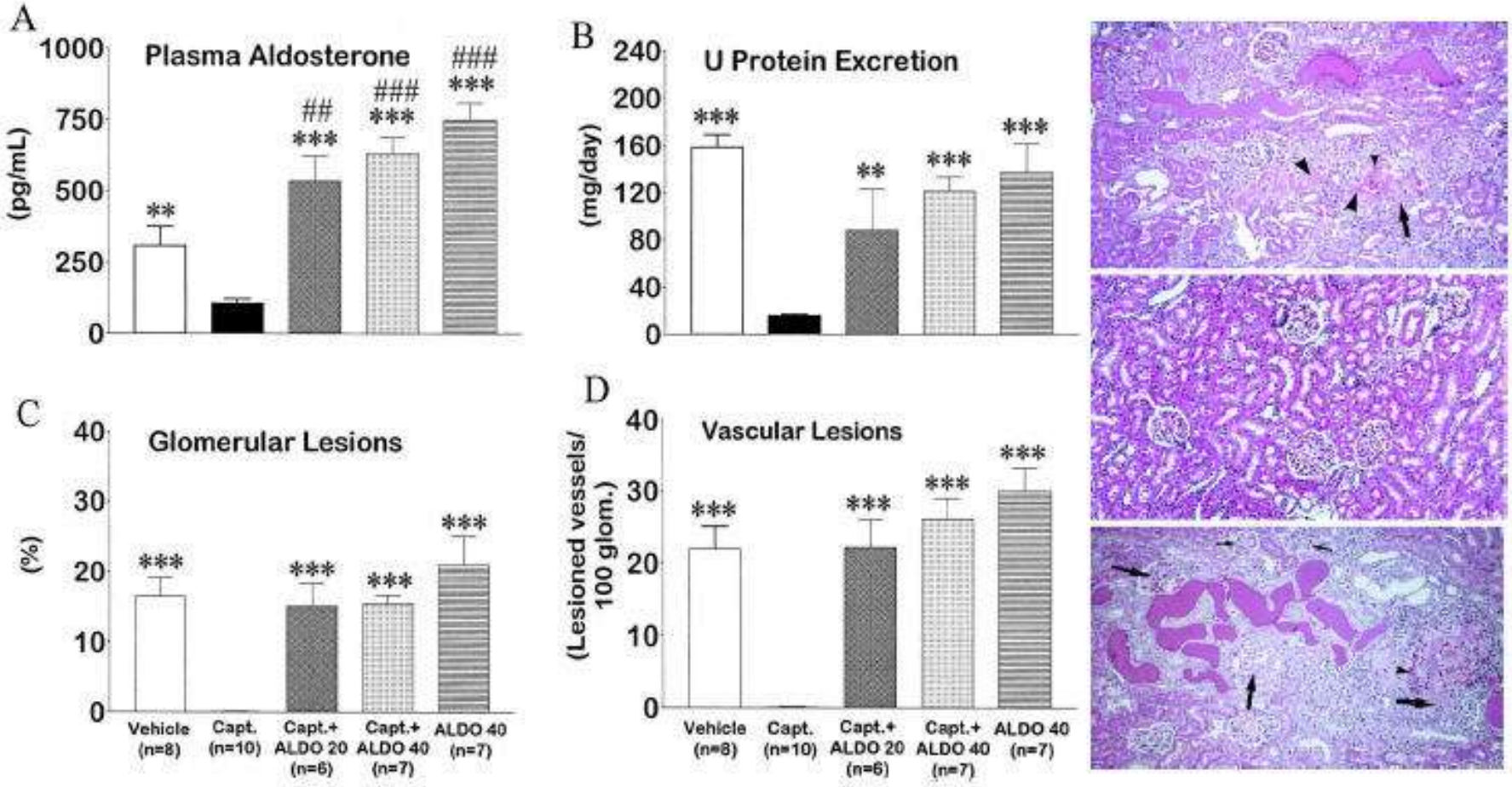
Effect of aldosterone on renal function in SHRSP rats



(Hypertension, 1999)

These findings support a major role for aldosterone in the development of malignant nephrosclerosis in saline-drinking SHRSP, independent of the effects of blood pressure. **(*Hypertension*. 1999;33[part II]:232-237.)**

Aldosterone antagonism :

- Diuretics have generally not been considered to have an antiproteinuric effect despite reductions in blood pressure .

- However, aldosterone antagonists appear to reduce proteinuria when used alone ,and to have an additive effect on proteinuria when used in combination with an ACE inhibitor or an ARB in both type 1 and type 2 diabetes.

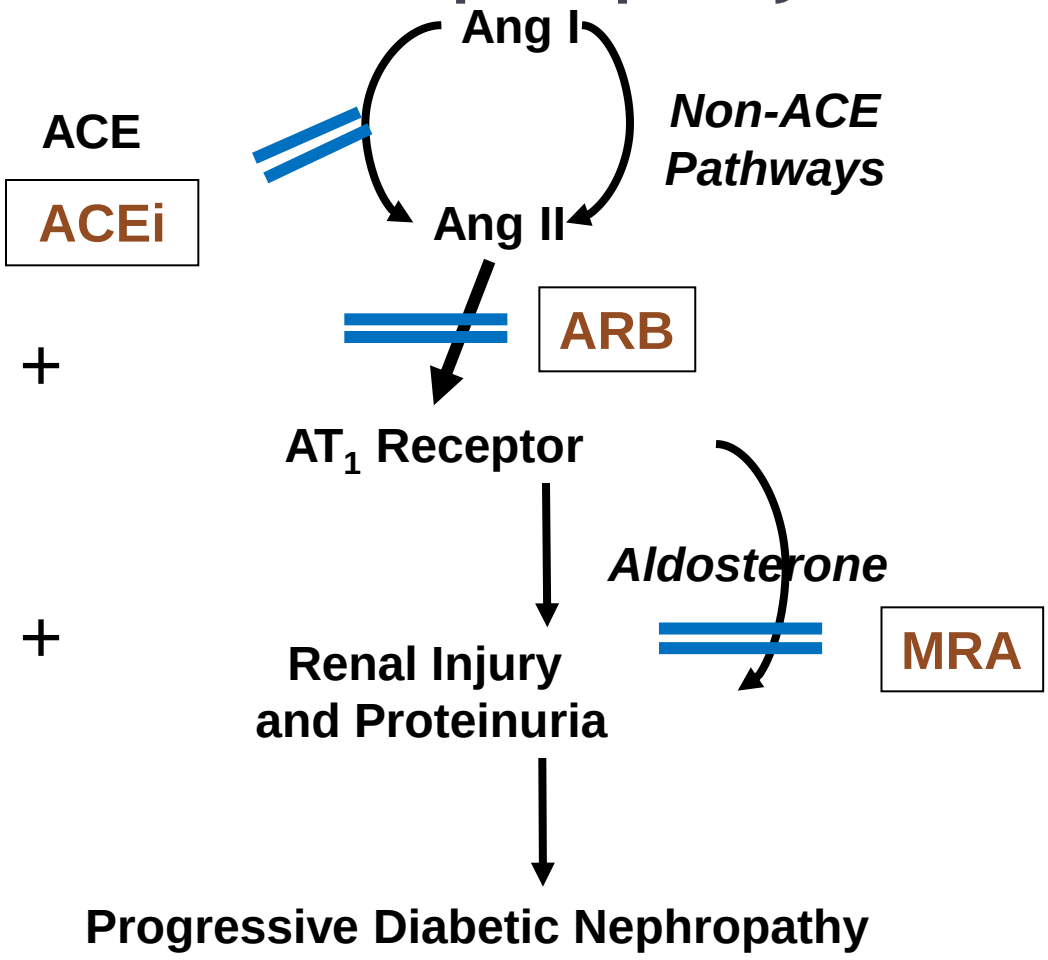
CJASN July 2006 vol. 1 no. 4 668-677

- There are no long term data regarding benefit with the combination of ACE inhibitor or ARB and aldosterone blockade in terms of slowing the rate of loss of GFR.

- The risk of inducing or aggravating hyperkalemia in patients with long-standing diabetic nephropathy may limit the use of aldosterone antagonists.

CJASN July 2006 vol. 1 no. 4 668-677

Can Dual Blockade of the RAAS Improve Renal Outcomes in Diabetic Nephropathy?



JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Addition of Angiotensin Receptor Blockade or Mineralocorticoid Antagonism to Maximal Angiotensin–Converting Enzyme Inhibition in Diabetic Nephropathy

Uzma F. Mehdi[*], Beverley Adams-Huet[*†], Philip Raskin[*], Gloria L. Vega[‡] and Robert D. Toto[*†]

« Previous | Next Article »
Table of Contents

This Article

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JASN December 1, 2009 vol. 20 no. 12 2641–2650

Abstract
» Full Text
Full Text (PDF)

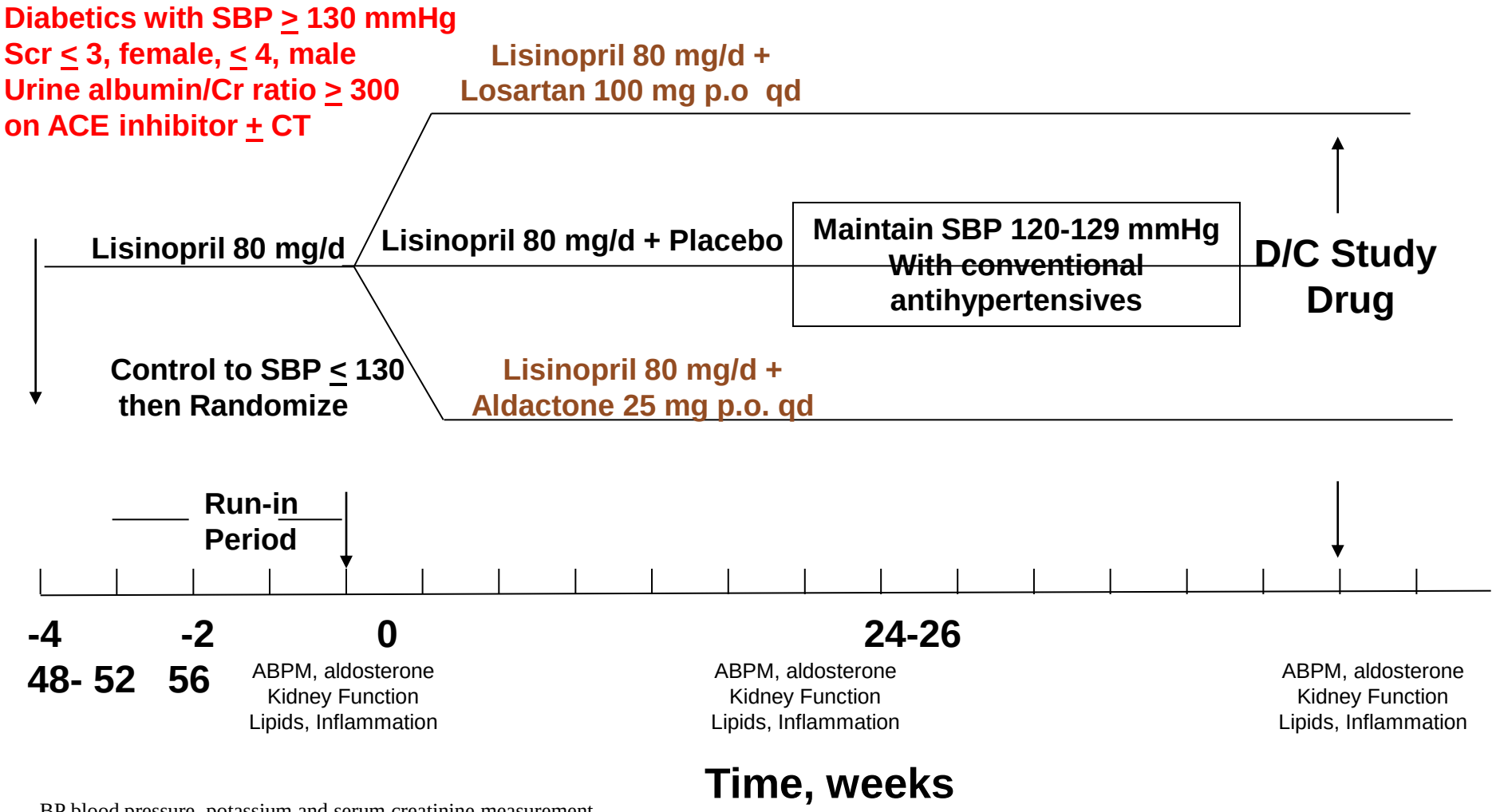
Combined Inhibition of the RAAS Pathway: ACEi + ARB vs ACEi + MRA in Diabetic Nephropathy

Study Design and Objectives

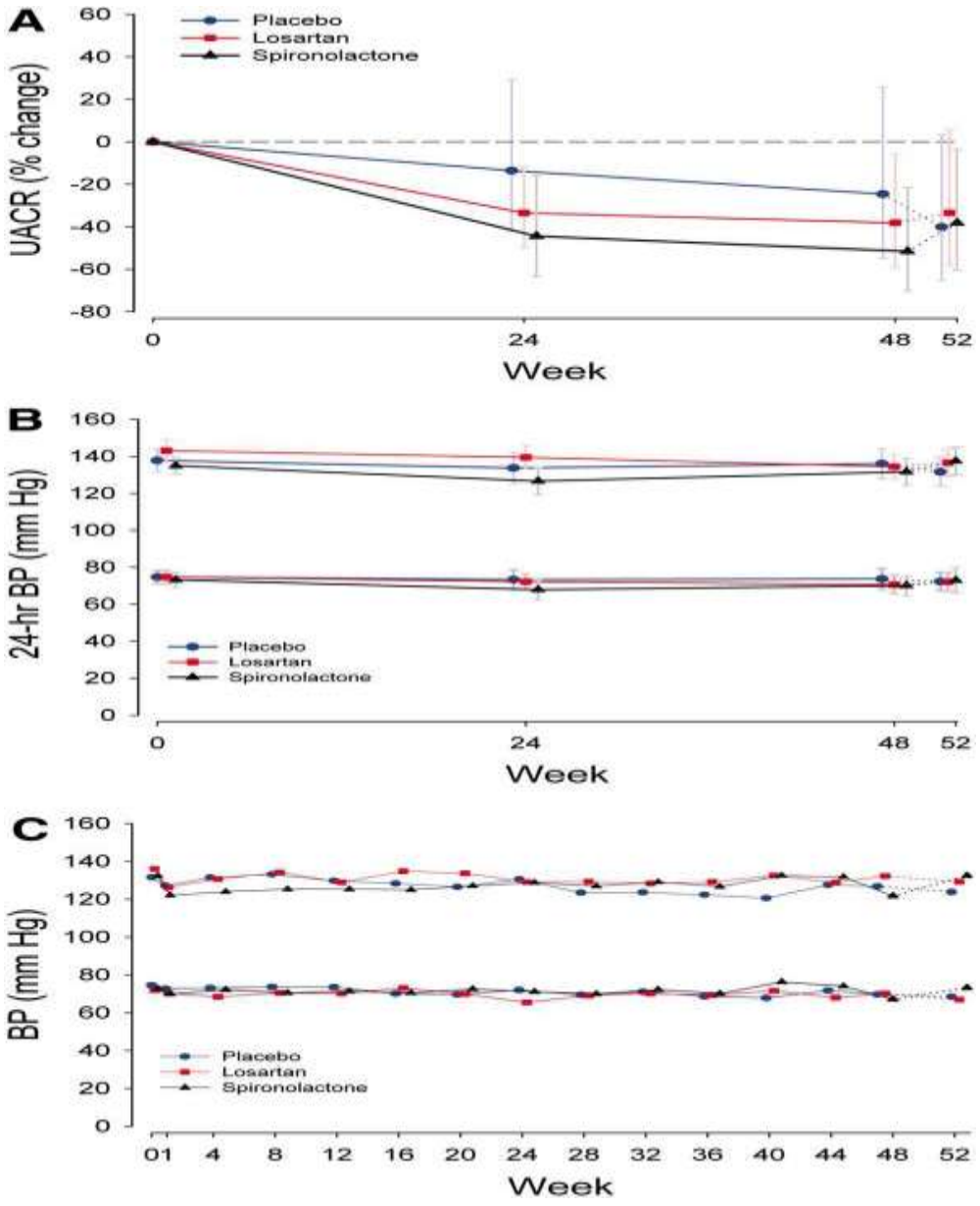
- Study Design: Randomized double-blind placebo controlled trial
- Study Population: Diabetics with macroalbuminuria despite maximally dosed ACE inhibitor
- Intervention: Lisinopril 80 mg/d + losartan 100 mg/d or + Aldactone 25 mg/d or + placebo
- Primary Outcome: Change in albuminuria
- Secondary Outcomes: Safety especially serum creatinine and hyperkalemia
- Follow up: 52 weeks

JASN 2009 Dec;20(12):2641-50

Combined Inhibition of the RAAS Pathway: ACEi + ARB vs ACEi + MRA in Diabetic Nephropathy



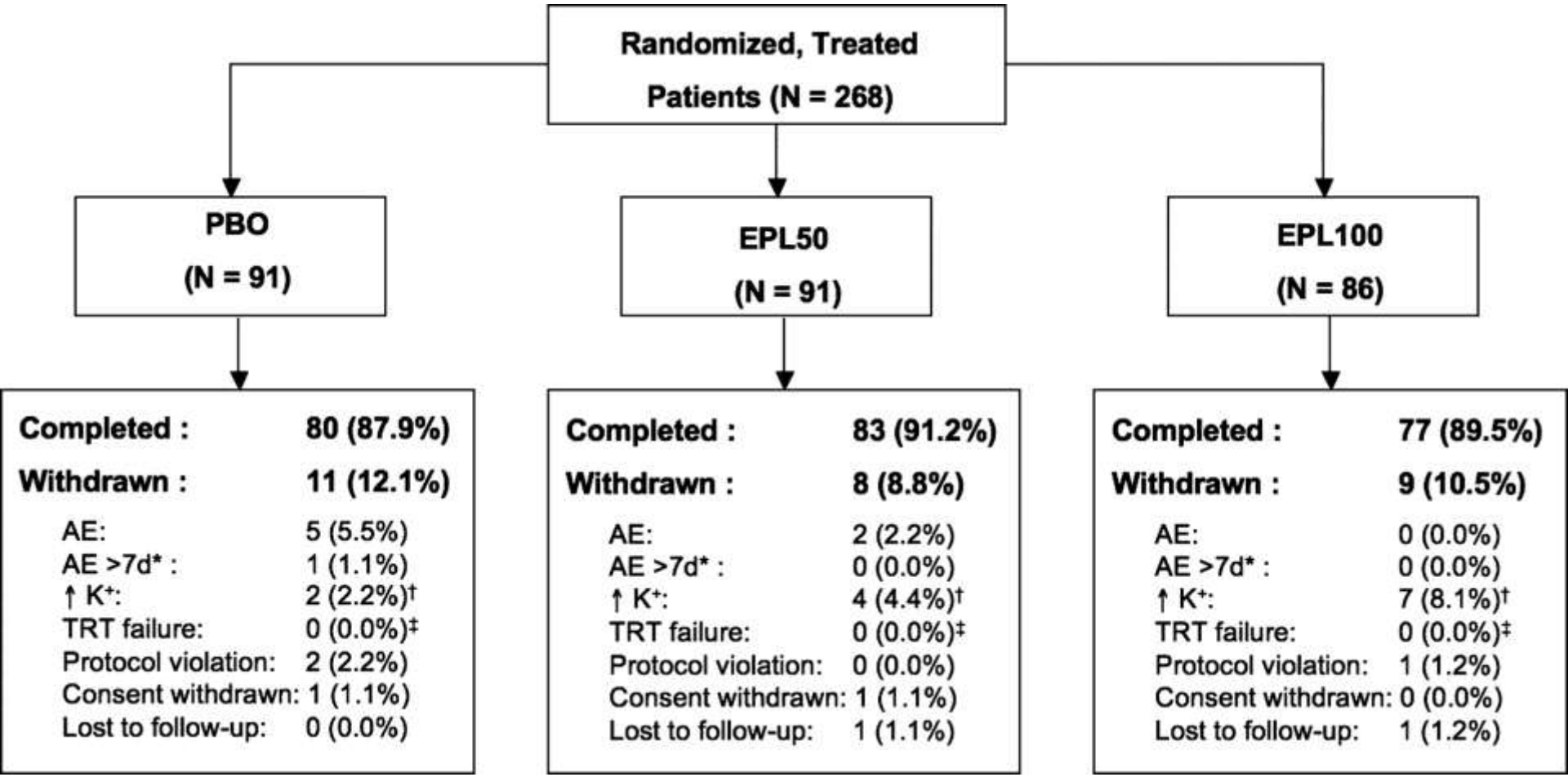
BP blood pressure, potassium and serum creatinine measurement
RF renal function-GFR, RPF, 24 hour urine sodium, creatinine,potassium, protein and urea



16.8% reduction: ACEi+ARB
34.0% reduction: ACEi+SPR

(J Am Soc Nephrol, 2009)

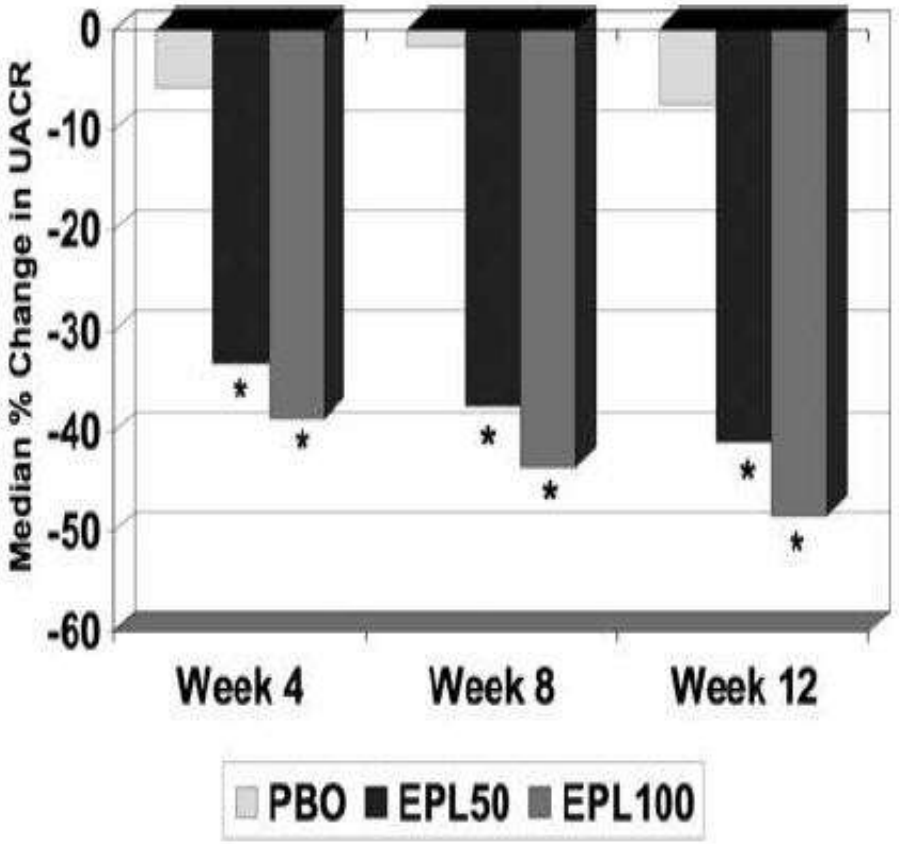
Selective Aldosterone Blockade with Eplerenone reduces albuminuria in patients with type 2 DM.



Epstein, M. et al. Clin J Am Soc Nephrol 2006;1:940-951

Clin JASN. 2006 Sep;1(5):940-51

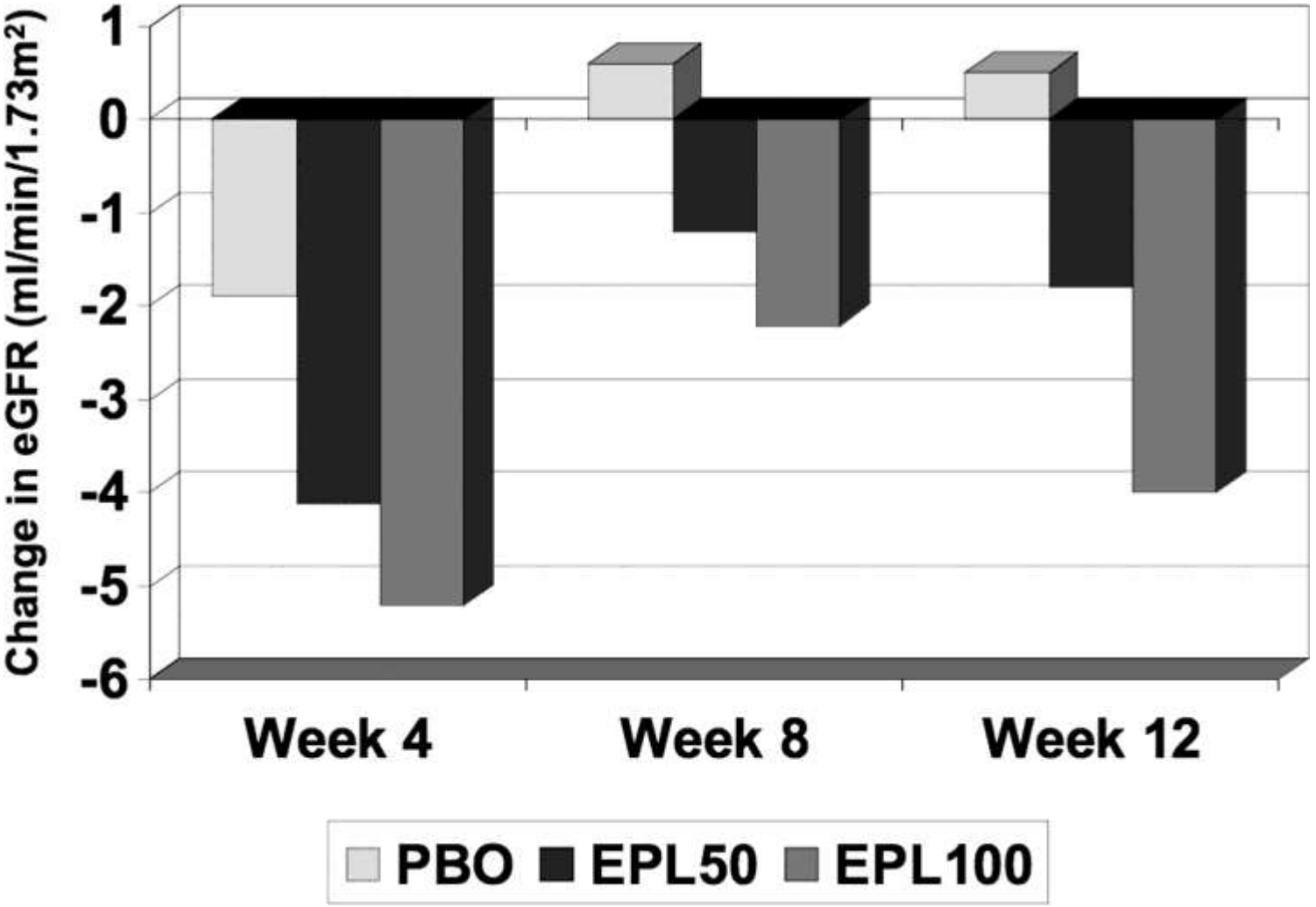
Effect of eplerenone combined with enalapril in type 2 diabetic nephropathy



Overall percentage change of UAER from baseline in type 2 diabetic patients

(J Am Soc Nephrol, 2006)

Overall absolute change from baseline eGFR over time by treatment group.



Epstein M et al. CJASN 2006;1:940-951

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conclusion

- Eplerenone, in doses of 50 or 100 mg added to the ACE inhibitor enalapril, results in a substantive and statistically significant reduction in albuminuria, as measured by UACR, in patients with type 2 diabetes.

- A dosing regimen of EPL50 with an ACE inhibitor may be preferable to EPL100 with an ACE inhibitor, because it confers the desired antialbuminuric benefit with a lesser risk for hyperkalemia

Am J Kidney Dis. 2008 Feb;51(2):199-211. doi: 10.1053/j.ajkd.2007.10.040.

Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review.

Bomback AS[1], Kshirsagar AV, Amamoo MA, Klemmer PJ.

Author information

[1]Department of Medicine, Division of Nephrology and Hypertension, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. abomback@unch.unc.edu

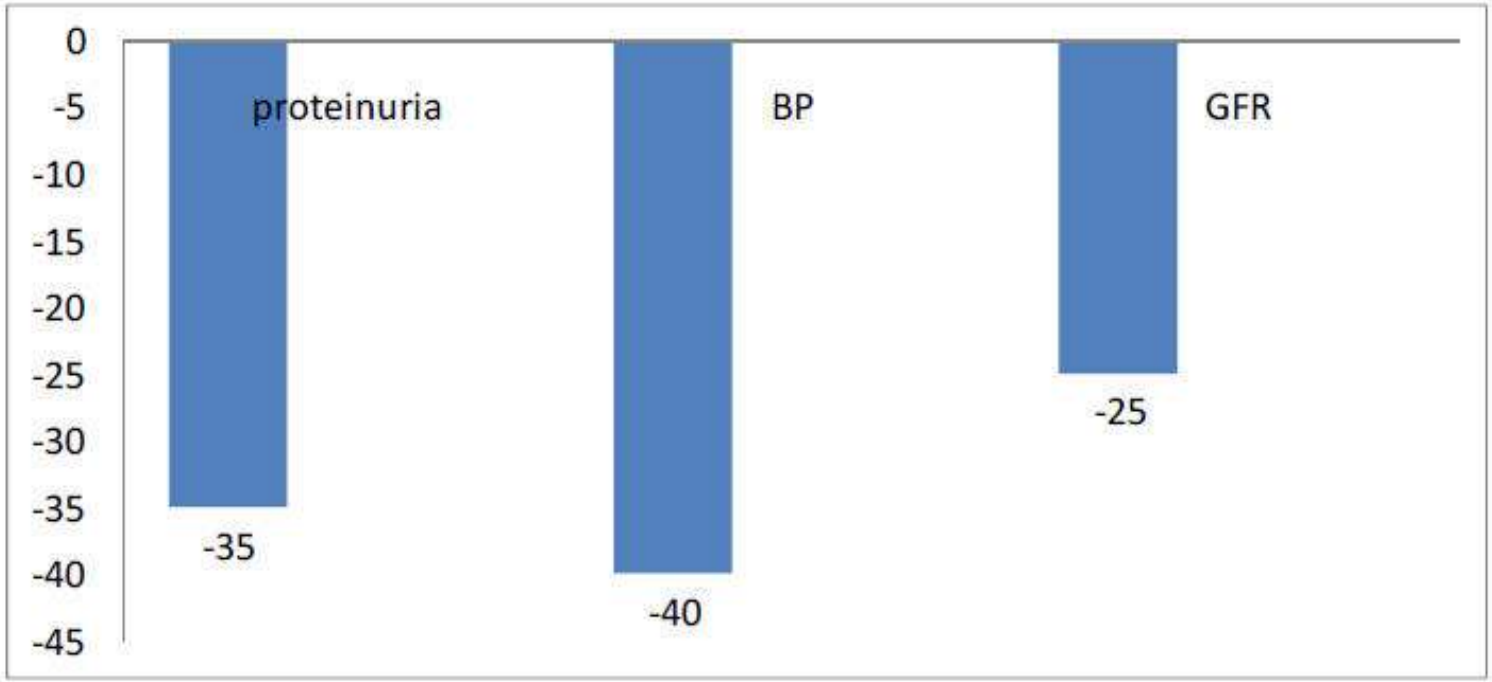
Abstract

BACKGROUND: The use of mineralocorticoid receptor blockers (MRBs) in patients with chronic kidney disease is growing, but data for efficacy in decreasing proteinuria are limited by a relative paucity of studies, many of which are small and uncontrolled.

OUTCOMES: Changes in proteinuria as the primary outcome; rates of hyperkalemia, changes in blood pressure, and changes in glomerular filtration rate as secondary outcomes.

RESULTS: 15 studies met inclusion criteria for our review; 4 were parallel-group randomized controlled trials, 4 were crossover randomized controlled trials, 2 were pilot studies, and 5 were case series. When MRBs were added to ACE-inhibitor and/or ARB therapy, the reported proteinuria decreases from baseline ranged from 15% to 54%, with most estimates in the 30% to 40% range. Hyperkalemic events were significant in only 1 of 8 randomized controlled trials. MRB therapy was associated with statistically significant decreases in blood pressure and glomerular filtration rate in approximately 40% and 25% of included studies, respectively.

Overview of effect of adding aldosterone antagonist to RAS blockade in CKD: Meta-analysis results



(Am J Kidney Dis, 2008)

Aldosterone
and Renal Tubular Acidosis

Aldosterone and Renal acidification

- Favors H+ and K+ secretion through enhanced sodium transport.
- Recruits more amiloride sensitive sodium channels in the luminal membrane of the collecting tubule.
- Enhances H+-ATPase activity in cortical and medullary collecting tubules.
- Aldosterone also has an effect on NH4+ excretion by increasing NH3 synthesis

Type 4 RTA (Hyperkalemic RTA)

- This disorder is characterized by modest HCMA with normal AG and association with hyperkalemia.
- This condition occurs primarily due to decreased urinary ammonium excretion.
- Hypoaldosteronism is considered to be the most common etiology.

Laing CM, Toye AM, Capasso G, and Unwin RJ. *Renal tubular acidosis: developments in our understanding of the molecular basis*. Int J Biochem Cell Biol 2005 Jun; 37(6) 1151-61

Laing CM and Unwin RJ. *Renal tubular acidosis*. J Nephrol 2006 Mar-Apr; 19 Suppl 9 S46-52

Type 4 RTA

Acquired Causes

- ↓ Renin:
  - Diabetic nephropathy
  - NSAIDS
  - Interstitial Nephritis
- Normal renin, ↓Aldo:
  - ACEs, ARBs
  - Heparin
  - Primary adrenal response

- ↓response to Aldo:
  - Medications: K+ sparing drugs (Sprinolactone), TMP-SMX, pentamidine, tacrolimus
  - Tubulointerstitial ds: sickle cell, SLE, amyloid, diabetes

- Int J Biochem Cell Biol 2005 Jun; 37(6) 1151-61

Treatment of Hyperkalemic RTA

- Treatment and prognosis depends on the underlying cause.
- Potassium-retaining drugs should always be withdrawn.
- Fludrocortisone therapy may also be useful in hyporeninemic hypoaldosteronism, preferably in combination with a loop diuretic such as furosemide to reduce the risk of extracellular fluid volume expansion.

Int J Biochem Cell Biol 2005 Jun; 37(6) 1151-61

Conclusion:

- Diabetic kidney is related to ESRD and CV deaths.
- Aldosterone may have a deleteroius effect on the diabetic nephropathy.
- Aldosterone antagonists play an important role in BP, UAE alone or in combinations with other RAAS blockade agents.
- Hypoaldosteronism is main cause for type 4 RTA.


Thank You